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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/929,771	08/14/2001	Robert T. Lum	96,877-V1	2294

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ART UNIT	PAPER NUMBER
1624	7

DATE MAILED: 09/09/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/929,771	LUM ET AL.	
	Examin r	Art Unit	
	Mark L. Berch	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *5/2/02* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *48-76* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *48-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 48-49, 68-72 are rejected under 35 U.S.C. 102(b) as being anticipated by Regnier.

See example 2, 27 and other purine examples which do not have a heterocycle attached at the 2-position. These correspond to $R_3 = NR_4 R_5$, and R_5 = optionally substituted lower alkyl. The compounds are anticancer agents.

The traverse is confused. Applicants repeatedly state that the prior art compounds "require a tricyclic heterocycle." This is not true. The heterocycle is a substituted piperidine, which is a monocyclic heterocycle so that the substituent thus falls within the definition of a substituted cycloheteroalkyl.

Claims 48-53, 56-57, 61, 64, 68-76 are rejected under 35 U.S.C. 102(a) as being anticipated by WO 97/16452.

Note formula I and species therein which deal with 6- (substituted anilino) species. The utility is the same. The claims in this case are broader than the disclosure of the 08/692012 parent and hence are only entitled at best to the date of 8/1/97.

It appears that an impasse has been reached on this point. Applicants insist that their claims are entitled to the "filing date" which is assumed to be the 8/2/1996 date of 08/692012. Applicants have not demonstrated this. As an example, in USP 5866702 (= 08/692012), column 2, lines 57-59, there is a proviso which excludes three compounds, three choices for R1-X. The current first proviso excludes one of these, the benzyl, but permits the other two. Thus, the current claim is broader. Note also the lettered points below. Also, note that the property of inhibition of IκB-α kinase is not in the parent 08/692012, so any method claim which relies just on such property is also not supported.

Claims 48-53, 56-57, 61, 64, 68-76 are rejected under 35 U.S.C. 102(b) as being anticipated by Norman.

The species named in the second paragraph of page 7431, column 2 is not subject to the proviso as it is a substituted benzyl. This species is NOT olomoucine. The utility is the same. As for the date issue, this was discussed above.

Claims 48-49, 51, 56, 76 are rejected under 35 U.S.C. 102(b) as being anticipated by McAfee.

See the list at Column 4 of the species, and note species 4. The new proviso does not exclude this species, which corresponds to R1 as thienyl.

Claims 48-49, 51, 56 are rejected under 35 U.S.C. 102(b) as being anticipated by Seyama.

See compounds 39 which corresponds to R_3 = substituted heteroaralkyl. Applicants traverse is not understood. The assert that heteroaralkyl is not a choice for R3. This is mistaken. See claim 48, 9th from last line 4th word. Second, applicants argue that this isn't a substituted heteroaralkyl, but that is also mistaken. It is a butyl group

substituted by a substituted purinyl group. Purine is certainly a heteroaryl group. See specification page 13, lines 13-14. Compound 35 is excluded by proviso.

The rejections made in the parent over Kaneko and WO 93/17020 are not included because R_2 = substituted heterocyclic and hydroxy-cyclopentyl respectively is no longer permitted. The rejection made in the parent over Breshears is not included because R_2 = H is no longer permitted. The rejections made in the parent over Bader and Liotta are not included because R_1' = halogen is no longer permitted.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 48-53, 56-57, 61, 64, 68-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vesely.

The reference discloses olomoucine, which the proviso removes from claim 1. However, the 6-(2-phenethylamino) derivative would be a chain homologue, with one carbon more in the chain. However, it has long been established that this type of difference --- varying the size of a chain --- constitutes a form of homology, and is a fact of very close structural similarity, rendering the homolog obvious. See *In re Shetty*, 195 USPQ 753; *In re Wilder*, 195 USPQ 426 and *Ex Parte Greshem*, 121 USPQ 422, all of which feature a compound with a C_2 link rejected over a compound with a C_1 link. Similarly, *In re Chupp*, 2 USPQ2d 1437 and *In re Coes*, 81 USPQ 369 have a C_1 link unpatentable over prior art showing C_2 link. Note also *In re Schaub,* 190 USPQ 324,

326, where compounds with C_5 and C_6 chains were called "adjacent homologs in the classic sense". *Ex parte Ruddy,* 121 USPQ 427 has a C_3 link unpatentable over a C_1 link. *Ex parte Nathan,* 121 USPQ 349 found the insertion of a C_2H_4 link obvious. In all of these cases, the variation was found to be obvious on the basis of close structural similarity; no secondary teaching was employed. In addition, the 6-(1-phenethylamino) choice would be the same as the prior art, just with an extra methyl on the α carbon of the benzyl. Compounds that differ only by the presence or absence of an extra methyl group or two are homologues. Homologues are of such close structural similarity that the disclosure of a compound renders *prima facie* obvious its homologue. The homologue is expected to be preparable by the same method and to have generally the same properties. This expectation is then deemed the motivation for preparing homologues. Of course, these presumptions are rebuttable by the showing of unexpected effects, but initially, the homologues are obvious even in the absence of a specific teaching to add or remove methyl groups. See *In re Wood,* 199 USPQ 137; *In re Hoke,* 195 USPQ 148; *In re Lohr,* 137 USPQ 548; *In re Magerlein,* 202 USPQ 473; *In re Wiechert,* 152 USPQ 249; *Ex parte Henkel,* 130 USPQ 474; *Ex Parte Fischer* 96 USPQ 345; *In re Fauque,* 121 USPQ 425; *In re Druey,* 138 USPQ 39. In all of these cases, the close structural similarity between two compounds differing by one or two methyl groups was itself sufficient show obviousness. See also MPEP 2144.09, second paragraph. The utility is the same.

Claims 48-53, 56-57, 61, 64, 68-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over De Azevedo.

The reference is from the January 1997 issue. It discloses roscovitine, shown in page 520. The same biochemical property is disclosed. The same issue arises as in the Vesely rejection. The date issue is as discussed above.

Claims 48-53, 56-57, 61, 64, 68-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over 6316456.

This is the US equivalent of the WO 97/20842 reference cited previously. The proviso has excluded the anticipating species. However, the rejected claims are still obvious. For example, species 10 differs only in that it has R9 as isopropyl, whereas the rejected claims have R9 as cyclopentyl. However, the reference teaches that exact equivalence, that R9 can be alkyl or cycloalkyl. Further, the last species of the Table 1 has just such a cyclopentyl moiety, thus providing a guidepost to this particular choice. Alternatively, the 7th species differs only in that it has the isopentenyl group rather than benzyl. Again the definition of R6 teaches that equivalence; see column 3, paragraph beginning at line 60, and many benzyl species are present.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 48-76 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. In R_1', optionally substituted with what? The remarks say that the specification defines these, but the examiner cannot locate any such definition. In this regard, note the comments made previously about defective definitions.
2. The use of "alkylthiol" e.g. ethanol, as a substituent in R_2 and R_3 is impossible. This is a molecule, and hence has no free valence, and so cannot be a substituent. The remarks state that it was fixed, but in nearly all places e.g. fourth from last line of page 2, it remains.
3. All the R_3 choices in claim 63 are garbled. It is impossible to know what these are. There is for example no such things as "histidinylol".
4. The use of "acetylene" in the R3 definition is improper because that is a molecule, not a moiety. Applicants traverse on the descriptive point H was correct. Thus, this point 4 can be fixed by reinstating the "ethynyl" claim language and that fix will not cause a descriptive problem under original point H.
5. A number of the claim 71 disorders are not considered a "cell proliferative disorder. a) Gout is a manifestation of hyperuricemia. Crystals of sodium urate cause acute inflammatory arthritis. It is not treated with antiproliferative agents. Symptoms are treated with anti-inflammatory agents. Gout itself is treated with **Colchicine , a microtubule inhibitor which appears to inhibit migration of white cells to affected joints and Allopurinol which is a competitive inhibitor of xanthine oxidase and thus causes excretion of hypoxanthine and xanthine**

instead of conversion to urate. b) Multiple Sclerosis is of unknown cause, although it may be of immunological origin. It is not characterized by cell proliferation, but is a destruction of the preformed myelin. Treatment does not involve standard antiproliferative agents, but instead involves the use of corticosteroids, and even that is for symptom relief; it does not treat the underlying disorder. c) Similarly, lupus (SLE is assumed) arises from hyperactivity of the immune system. d)Similarly, "host-vs.-graft disease" is not normally considered a cell proliferation disease, but is more or less an expected response to foreign lymphocytes, when the body is unable to reject them. e) Type I diabetes is a disorder of the carbohydrate mechanism caused by little or no endogenous insulin. It is correct that lymphocytes destroy the beta-cells in the islets of Langerhans, whereas the lymphocytes should not do that. This does not mean that Type I diabetes is a "cell proliferative disorder". f) Rheumatoid arthritis is generally classified as an autoimmune disorder, but applicants seem to be assuming that any autoimmune disease by its very nature is a "cell proliferative disorder", which is simply not true. The traverse here appears to completely misunderstand the meaning of "cell proliferative disorder." A cell proliferative disorder is anything that causes any abnormal cell growth. That can be growth by cellular proliferation more rapidly than normal, or continued growth after the stimulus that initiated the new growth has ceased, or lack (partial or complete) of structural organization and/or coordination with surrounding tissue. The remarks seem to indicate that applicants are using a vastly broader definition, in which "cell proliferative disorder" is any disorder in which the proliferation of cells is part of the body's response. It is correct that there

is cell growth e.g. monocytes in the case of gout in the body's response to the urate crystals. But that does not make it a "cell proliferative disorder" according to the normal understanding of the term. If applicants definition of the terms were to be used, nearly all diseases will qualify as a "cell proliferative disorder" , since nearly all involve some sort of cell growth.

6. Claim 48, page 3, line 10, there is a semicolon after "or" which makes no sense.
7. Also, the second "or" on that line resumes what list? Both previous lists, the R_3 definition, and the R_4/R_5 definition lists have already been closed with their own "or" words, so this material, starting at ninth from last line of claim 48, has no clear role. It is assumed that the "or" continues the R3 definition, but that is by no means clear, since there was previously already an "or" on the first line of the R3 definition.

Claim 68 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

There is no practical way to determine what the scope of claim 68 is. It is entirely possible that the claim covers all known diseases. Determining whether a given disease responds or does not respond to such inhibition will surely involve undue experimentation. Suppose that a given Inhibitor X when administered to a patient with Disease D does not obtain a response. Does one then conclude that Disease D does not fall within this claim? Keep in mind that:

A. It may be that the next patient will respond. It is quite common for pharmaceuticals to work only with some people, not all. Thus, how many need to be tested?

B. It may be that the wrong dosage or dosage regimen was employed. It is quite common for pharmaceuticals to work at one dosage, but not at another which is significantly higher or lower. Furthermore, the dosage regimen may be vital --- should the drug be given e.g. once a day, or four times in divided dosages? Thus, how many dosages and dosage regimens must be tried before one is certain that this pharmaceutical won't affect Disease D?

C. It may be that X simply isn't potent enough for Disease D, but that another inhibitor Y is potent enough, so that D really does fall within the claim. Thus, how many different inhibitors must be tried before one concludes that D doesn't fall within the claim?

D. Conversely, if D responds to Y but not to X, can one really conclude that D falls within the claim? It may be that the X result is giving the accurate answer, and that the success of Y arises from some other unknown property which Y is capable of. Thus, when mixed results are obtained, how many more pharmaceuticals need be tested?

E. Finally, suppose that X really will work, but only when combined with Z. There are for example, agents in the antiviral and anticancer technology which are not themselves effective, but the disease will respond when the agents are combined with something else.

F. In addition, there are many, many known cell cycle kinase inhibitors, affecting a number of different kinases. One would have to test all of them to determine that a given disease does not fall within the claim. And there are dozens, possibly hundreds of different kinases which must be checked, because there are many phases involved in cell proliferation. For example, in mitosis, the division of a cell's nucleus there is the

Prophase, Prometaphase, Metaphase, Anaphase, and Telophase processes, and that is just part of M-phase.

As a result, determining the true scope of the claim will involve extensive and potentially open-ended research. Without it, one skilled in the art cannot determine the actual scope of the claim. Hence, the claim is indefinite. The traverse does not comes to terms with the rejection. It says that it covers "only those diseases attributable to the undesired proliferation of cells." No such limitation actually appears in claim 68, which makes no mention of proliferation.

Claims 48-76 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The following issues still remain:

B. The replacement of "thio" with "mercapto" in R_3 is new matter. The term "thio" is a generic one, indicating the presence of sulfur in some form. As a substituent, it has no one single generally accepted meaning. There could be intended thioxo (=S) or mercapto (-SH). It can also denote replacement by S of some other atom (normally, oxygen or carbon) as in "thioalkoxy", where O is replaced by S. Perhaps some term which began with "thio", like thiophene was intended. The selected choice must be supported by the specification, showing that one of ordinary skill in the art, reading the specification, would have been sure that this is what was originally intended. The traverse is not understood. Page 11, line 10 says that thiol and mercapto mean the same thing, but R3 was listed as thio, not thiol.

C. The choice of "substituted aralkyl" in R_1' lacks description in the specification. While many other R_1' choices are specified as being optionally substituted, this one is not.

D. The same problem occurs in R_2; aralkyl is not permitted to be substituted. The traverse on this misses the point. The issue here isn't that the specification lacks a definition for aralkyl; none would be needed for this conventional terms. It's that aralkyl, permitted as a choice for certain variables, e.g. R4 and R5, isn't permitted for R_1' and R_2.

E. The three provisos lack description. Even a negative limitation requires description, *Ex Parte Grasselli,* 231 USPQ 393. The claims originally had several provisos, but the new one does not appear to be on the original list, nor does it appear to be a combination of any of several of the original provisos. The traverse is unpersuasive. Even if the proviso were not to expand the claim, it still needs description; note the fact situation in *Grasselli,* where the proviso did not expand the claims. There is nothing remotely suggesting the concepts of these provisos.

F. The claim has been expanded because some of the original provisos have been removed. For example, in USP 5866702 (= 08/692012), column 2, lines 57-59, there is a proviso which excludes three compounds, three choices for R1-X. The current first proviso excludes one of these, the benzyl, but permits the other two. Thus, the current claim is broader, permitting things originally barred.

G. The "alkoxy" of page 3, line 1 is broader than the specification, which has "lower alkoxy" at page 13, line 3, 16, etc. Likewise in the R_3 definitions. The correction made was at a place which did not need it. Applicants' question --- "why is the term alkoxy not permitted by the specification? --- may be misunderstanding the rejection. At those

places, the specification does not teach alkoxy, it teaches only the narrower lower alkoxy. Thus, e.g. page 13, line 3 has "lower alkoxy" and not the broader "alkoxy".

I. The substituent list at page 2, line 8 is not supported for the choice of heteroarylalkyl, because several items on that line (amino, amido, carboxy, etc) are not present on page 14, lines 8-10. Likewise in the R_3 definitions. The traverse is unpersuasive. Applicants state "the claims are part of the specification". This is true, but these are not original claims. If applicants believe that the material was in the original claims, they must locate that exact text, and then add it back to the specification proper, which would fix the problem.

K. The utility in claim 68 lacks description in the specification. Where does the specification say that these compounds can be used to treat any disease alleviable by treatment with any cell cycle kinase inhibitor? That literally covers treatment of every disease which is treatable by any cell cycle kinase inhibitor, even one unrelated to the ones here, even inhibitors which have no effect on CDK2 or IκB-α (which are the only kinases mentioned), and even ones which are vastly more potent than the compounds here, and even compounds which have additional properties which are actually responsible for the potency. The traverse is unpersuasive. The text to which applicants point is very different from the claim language. The claim language refers to <u>any</u> disease "alleviable by treatment with a cell cycle kinase inhibitor" --- any inhibitor. The page 1 text only refers to "autoimmune diseases" and "proliferative diseases where pathogenesis involves abnormal cell proliferation". Those are the only categories mentioned. The current claim language would cover any disease, even those outside

those two categories, provided that some cell cycle kinase inhibitor – even one vastly more potent than applicants', even one that hasn't been invented yet, can alleviate it.

M. The scope of claim 70 lacks description in the specification. The traverse is unpersuasive. The closest to this claim language is "proliferative diseases where pathogenesis involves abnormal cell proliferation" which is a little narrower; claim 70 is not limited to proliferative diseases.

N. The choice of substituted heteroaralkyl in R_2 and in R_3 lacks description in the specification. See page 5, line 9, and page 6, line 2. The paragraphs list substituted choices for certain ones, but not for this one. The fact that the term is defined in the specification does not mean that it is a described choice for these particular variables.

Claim 70 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

A proliferative disorder is anything that causes any abnormal tissue growth. That can be growth by cellular proliferation more rapidly than normal, or continued growth after the stimulus that initiated the new growth has ceased, or lack (partial or complete) of structural organization and/or coordination with surrounding tissue. It can be benign or malignant. Thus, such a term covers not only all cancers, but also covers precancerous conditions such as lumps, lesions, and polyps. In addition, it embraces various non-cancerous proliferative disorders such as certain types of restenosis, vascular smooth muscle proliferation associated with atherosclerosis, glomerular nephritis, clonal proliferative disorders including the various Myelodysplastic

Syndromes such as Refractory anemias, certain types of abnormal wound healings, different types of abnormal angiogenisis, pulmonary fibrosis, macular degeneration, myeloproliferative disorders such as primary polycythemia and myleofibrosis, and rheumatoid arthritis. There is no such thing that an agent which is effective against such disorders generally, since they are so diverse, nor is there any reason to think that such an agent could be made to work.

When the best efforts have failed to achieve a goal, it is reasonable for the PTO to require evidence that such a goal has been accomplished, *In re Ferens*, 163 USPQ 609. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006.

The traverse is unpersuasive. Applicants state that "the invention consist of compounds that inhibit CDK2 and IκB-α." However, the notion that all abnormal tissue growth involves these two is contrary to what is known. For example, the first step is the progression from G0 to G1, in which CDK-2 has no role. Further, the actual cell division itself takes place during M-phase. This has both Mitosis, the division of a cell's nucleus , including the Prophase, Prometaphase, Metaphase, Anaphase, and Telophase processes, as well as cytokinesis, the division of the cytoplasm, which results when a fiber ring composed of actin around the center of the cell contracts, pinching the cell into two daughter cells, each with one nucleus. CDK-2 has nothing at all to do with this M-phase. Thus, if a disorder involved either of these steps, a CDK-2 inhibitor would be totally irrelevant. With regard to inhibition of IκB-α, it is not clear how that is relevant to the alleged utility.

Claim 72 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claim sets forth the treatment of cancer generally. However, there never has been a compound capable of treating cancer generally. There are compounds that treat a range of cancers, but no one has ever been able to figure out how to get a compound to be effective against cancer generally, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. Even the most broadly effective antitumor agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-1), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task. Applicants cite cisplatin, antimetabolites, etc which "have all been used to treat more than one type of cancer." This is true, but none of these can be used to treat cancer generally, or anything even remotely close to that, which is what these claims call for. In fact, there are many, many kinds of cancer which do not appear to respond to chemotherapy at all. Just as an example, many forms of CNS cancers cannot be treated

with chemotherapy. This is because 1) the blood-brain barrier, which is often intact in parts or all of a brain tumor, will block out many drugs, as it is the purpose of the blood-brain barrier to protect the brain from alien chemicals, and 2) CNS tumors are characterized by marked heterogeneity, which greatly decreases vulnerability to chemotherapy. As a result, many categories of CNS tumors simply have no chemotherapy available. These include, generally, hemangiomas and hemangioblastomas, low grade gliomas, meningiomas, craniopharyngiomas, acoustic neuromas, pituitary adenomas, optic nerve gliomas, glomus jugulare tumors and chordomas, to name just some. Further, this specification fails to actually name which cancer(s) these compounds would be expected to be effective against. Since there are no established anticancer agents structurally related to these compounds, this lack of disclosure places an improper burden on the public to figure out how to use the compounds. The sole testing done in this regard appears on page 50. At 3 dosage regimens, the tested species met the minimum standard of efficacy, T/C = 130. However, compound 3 is by far the most potent as noted below. In terms of the ability to inhibit cell proliferation, the next most potent compound tested had only 1/6 its potency and hence would not be expected to pass even this crude screening test with L1210. The evidence of record is thus that this compound is not representative of the genus as a whole; it is by far the most potent, in terms of CDK2.

Claim 75 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The scope of treating inflammation generally is extraordinarily broad. Inflammation is a process which can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. It is one of the most pervasive of all body processes. Inflammation is a very general term which encompasses a huge variety of specific processes.

Inflammation is the reaction of vascularized tissue to local injury; it is the name given to the stereotyped ways tissues respond to noxious stimuli. These occur in two fundamentally different types. Acute inflammation is the response to recent or continuing injury. The principal features are dilatation and leaking of vessels, and recruitment of circulating neutrophils. Chronic inflammation or "late-phase inflammation" is a response to prolonged problems, orchestrated by T-helper lymphocytes. It may feature recruitment and activation of T- and B-lymphocytes, macrophages, eosinophils, and/or fibroblasts. The hallmark of chronic inflammation is infiltration of tissue with mononuclear inflammatory cells. Mechanistically, chronic inflammation encompasses a broad spectrum of immunologic processes, including antibody formation, antibody-dependent cell-mediated cytotoxicity, and cell-mediated immunity (delayed-type hypersensitivity). Granulomas are seen in certain chronic inflammation situations. They are clusters of macrophages which have stuck tightly together, typically to wall something off. Granulomas can form with foreign bodies such as aspirated food, toxocara, silicone injections, and splinters.

Otitis media is an inflammation of the lining of the middle ear and is commonly caused by Streptococcus pneumoniae and Haemophilus influenzae. Cystitis is an

inflammation of the bladder, usually caused by bacteria. Blepharitis is a chronic inflammation of the eyelids that is caused by a staphylococcus. Dacryocystitis is inflammation of the tear sac, and usually occurs after a long-term obstruction of the nasolacrimal duct and is caused by staphylococci or streptococci. Preseptal cellulitis is inflammation of the tissues around the eye, and Orbital cellulitis is an inflammatory process involving the layer of tissue that separates the eye itself from the eyelid. These life-threatening infections usually arise from staphylococcus. Hence, these types of inflammations are treated with antibiotics.

Cholecystitis is gallbladder inflammation usually caused by a gallstone that cannot pass through the cystic duct. In those cases, it normally cannot be treated by pharmaceuticals but instead the gallbladder is removed. Cholecystitis without the formation of gallstones, called acalculous cholecystitis, is caused by bacteria such as Salmonella, Staphylococcus, Streptococcus (as part of scarlet fever), and leptospirosis, and thus may be treatable by treating the underlying infectious agent. Acute inflammation of the gall bladder can also arise from typhoid; treatment is with antibiotics.

In gout, joint inflammation is caused by the formation of monosodium urate monohydrate (MSU) crystals within the joint space. Acute attacks of gout are treated with colchicine (to inhibit of MSU-induced chemotactic factor release by PMNs) and after the acute phase with allopurinol to control the blood levels of uric acid. Pseudogout, sometimes referred to as calcium pyrophosphate disease (CPPD), is inflammation caused by calcium pyrophosphate (CPP) crystals. It is treated with nonsteroidal anti-inflammatory drugs , corticosteroids and Colchicine.

Sinusitis is the inflammation of the mucosal lining of one or more of the 4 cavities near the nasal passages (ethmoid, maxillary, frontal, and sphenoid sinuses). It commonly accompanies upper respiratory viral infections which obstruct the opening, but such obstruction can also arise from abnormalities in the structure of the nose, enlarged adenoids, diving/swimming, infections from a tooth, trauma to the nose, and foreign objects that are stuck in the nose. Bacteria, notably Streptococcus pneumonia, Haemophilus influenza, and Moraxella catarrhalis grown in the trapped secretions. In most cases it requires no treatment, but antibiotics may be given, along with acetaminophen for pain and nosedrops, for relief of symptoms.

Pharyngitis is infection and inflammation of the throat (including the nasopharynx, uvula, and soft palate)and tonsillitis is of the tonsils. These are caused by a variety of viruses (adenoviruses, influenza viruses, parainfluenza viruses, Epstein-Barr virus, enteroviruses, Herpes simplex virus), mycoplasmas (e.g. Mycoplasma pneumoniae), and bacteria (Group A Beta Hemolytic Streptococci (GABHS), Streptococcus pyogenes, Neisseria Gonorrhea, Hemophilus Influenza Type B) as well as fungal infections, parasitic infections, cigarette smoke, and unknown causes.

Similarly, Osteomyelitis is the inflammation of bones, generally caused by bacteria (most commonly Staphylococcus Aureus). The disease can be caused by fungi or viruses. Dacryoadenitis, an inflammation of the tear gland, can arise from infectious mononucleosis, mumps, gonorrhea, or influenza. Conjunctivitis (pink eye) is inflammation of the conjunctiva and can be caused by many microorganisms, including staphylococci, Haemophilus influenzae, streptococci, gonococci, and viruses such as

adenoviruses. Treatment in all of these cases, when possible, is thus to the underlying infectious agent.

Rheumatoid arthritis is an inflammatory bone disease causing destruction of articular cartilage, in which macrophages accumulate in the rheumatoid synovial membrane. Mediators are cytokines, including IL-1, IL-18, TNF-α and IFN-γ.

Pneumonia is an inflammation of the lungs. Lobar pneumonia affects one or more sections (lobes) of the lungs. Bronchial pneumonia (or bronchopneumonia) affects patches throughout both lungs. Bacterial pneumonia is caused by various bacteria notably Streptococcus pneumoniae. Viral pneumonia is caused by viruses (such as respiratory syncytial, parainfluenza, and influenza), Other causes are fungi, mycoplasmas, rickettsias (especially Q fever), Chlamydia, or parasites. It can also occur as a hypersensitivity, or allergic response, to agents such as mold, humidifiers, and animal excreta, and in such a case would be treated with anti-allergic agents. Treatment may include antibiotics for bacterial pneumonia. Antibiotics may also speed recovery from mycoplasma pneumonia and some special cases. There is no clearly effective treatment for viral pneumonia.

Adult (or Acute) Respiratory Distress Syndrome (ARDS) is severe inflammation in both lungs resulting in an inability of the lungs to function properly. ARDS is a devastating, often fatal, inflammatory lung condition that usually occurs in conjunction with catastrophic medical conditions, such as pneumonia, shock, sepsis, and trauma. No specific therapies currently exist for ARDS patients. Treatment primarily involves supportive care in an intensive care unit , including use of a mechanical ventilator and supplemental oxygen to help patients breathe.

Chronic bronchitis is a long-term inflammation of the bronchi, which results in increased production of mucus, as well as other changes. Chronic bronchitis has no specific organism recognized as the cause of the disease. Cigarette smoking is cited as the most common contributor to chronic bronchitis, followed by bacterial or viral infections and environmental pollution. Treatment may include bronchodilators for inhaled medications, oxygen supplementation, lung reduction surgery and lung transplantation.

Acute bronchitis is the inflammation of mucous membranes of the bronchial tubes and is usually caused by infectious agents such as bacteria or viruses. It may also be caused by physical or chemical agents -- dusts, allergens, strong fumes -- and those from chemical cleaning compounds, or tobacco smoke. (Acute asthmatic bronchitis may happen as the result of an asthma attack, or it may be the cause of an asthma attack.) Acute bronchitis is usually a mild, and self-limiting condition, with complete healing and return to function. Most of the treatment is supportive of the symptoms, and may include analgesics, such as acetaminophen for fever and discomfort.

Asthma is a chronic, inflammatory lung disease involving recurrent breathing problems. It is characterized by three airway problems: obstruction, inflammation, and hyper-responsiveness. These lead to contraction of airway muscles, mucus production, and swelling in the airways. There are many different asthma triggers.

Myocarditis is an inflammation of the muscular middle layer of the heart (myocardium) Viruses, bacteria, and noninfectious diseases can cause it. Treatment is primarily supportive e.g. drugs may be used to improve the heart's ability to contract

and to remove extra fluids from the body. Unless the underlying infectious agent itself is treatable, this inflammation is not itself treated.

Glossitis is inflammation of the tongue. Local causes of glossitis include bacterial or viral infection, mechanical irritation or injury from burns, rough edges of teeth or dental and oral appliances, or other trauma; exposure to irritants (tobacco, alcohol, hot foods, or spices), and sensitization (to e.g. toothpaste, mouthwash, breath fresheners, dyes in candy, plastic in dentures or retainers) anemia and other B vitamin deficiencies, erythema multiform, pemphigus vulgaris, syphilis, and other disorders. It can be inherited. Corticosteroids such as prednisone may be given to reduce the inflammation. Antibiotics, antifungal medications, or other antimicrobials may be prescribed if the cause of glossitis is an infection. Anemia and nutritional deficiencies must be treated, often by dietary changes or other supplements.

Meningitis is the inflammation of the meninges—the surrounding 3-layered membranes of the brain and spinal cord, and the fluid it is bathed in, (CSF). It can be caused by virtually any known infectious agent. Thus, if it is caused by Haemophilus influenzae or Neisseria meningitis, the antibiotic derivative rifampin would be used.

Myelitis is inflammation of the spinal cord.

Encephalitis is inflammation of the brain itself, often caused by a group of arboviruses. Treatment of encephalitis is largely supportive because no specific antiviral agents, except for that which works against herpes simplex virus, are available for therapy.

Inflammation in the brain is an significant component of some important neurodegenerative conditions, including Alzheimer's Disease, AIDS dementia, Pick's

Disease, Parkinson's Disease, and Huntington's Disease. The circumstances here are poorly understood because while there does not appear to be lympho-infiltrative processes, there is neuropathological evidence for immune activation. Thus, inflammation may be a disease-aggravating or even a disease-ameliorating factor in pathogenesis, or a
non-contributory consequence of the injurious cascade of neurodegeneration and thus incidental.

Hepatitis is an inflammation of the liver, usually caused by viral invasion, notably hepatitis A, B and C, but sometimes Epstein-Barr virus; herpes simplex viruses; measles, mumps, and chicken pox viruses; and cytomegaloviruses. Treatment, when possible, is with antivirals. Inflammation of the liver also take the form of alcoholic hepatitis. Lupoid hepatitis is an autoimmune disorder.

Hemorrhoids is an enlarged or varicose condition of the hemorrhoidal veins and tissues around the anus, either internal or external. Anything which obstructs the free circulation of the blood in the portal system will give rise to hemorrhoids. Constipation, straining at stool, diarrhea, dysentery, rough toilet paper, uncleanliness, pelvic tumors, displacement of the uterus and pregnancy are among the most common causes.

There is a series of inflammatory problems directly connected to neutrophil-endothelial cell adhesion (NECA). These include frostbite injury, bacterial meningitis, acute airway inflammation, allograft rejection, hemorrhagic shock, septic shock, ischemia and reperfusion injuries.

Urethritis is an inflammation of the duct that leads from the bladder to the body's exterior. It is often due to fecal contamination or irritation due to physical or chemical

substances (e.g. introduction of foreign bodies into the urethra, bubble bath, or soap) or gonorrhea. Treatment may simply involve the withdrawal of the offending chemical agent, or the administration of antibiotics, when Neisseria gonorrhoeae is involved.

Inflammation can arise from the eruption of teeth in a child (teething).

Inflammation of the nails can arise from chronic paronychia, fungus (especially Candida albicans), trauma, impaired circulation, and dermatitis.

Bright's disease (or glomerulonephritis) is inflammation of the glomeruli and the nephrons, the structures in the kidney that produce urine. It usually results from an infection, such as a streptococcal infection, that occurs somewhere else in the body. There is no real treatment beyond relief of the symptoms.

Thyroiditis is an inflammation of the thyroid gland, and takes three forms. Hashimoto's Thyroiditis (chronic lymphocytic thyroiditis) is the most common type of thyroiditis. It is an autoimmune disorder, and treatment is to start thyroid hormone replacement. For De Quervain's Thyroiditis (subacute or granulomatous thyroiditis), treatment is usually bed rest and aspirin to reduce inflammation. Occasionally cortisone and thyroid hormone may be used. Silent Thyroiditis usually arises following pregnancy. Treatment is usually bed rest with beta blockers.

Regional enteritis (Crohn's disease or ileitis) is an autoimmune disorder which is associated with the presence of Mycobacterium paratuberculosis. It can affect any part of the gastrointestinal tract but most commonly affects the ileum. The inflammation is controlled primarily by regulation of diet, antibiotics if abscesses and fistulas are present, sometimes Prednisone and other corticosteroids, and surgery.

Another category of inflammatory disorders is Interstitial lung disease, or ILD, (interstitial pulmonary fibrosis), a term that includes more than 180 chronic lung disorders, which may be chronic, nonmalignant (non-cancerous) and noninfectious. Interstitial lung diseases are named after the tissue between the air sacs of the lungs called the interstitium -- the tissue affected by fibrosis (scarring). The common link between the many forms of ILD is that they all begin with an inflammation. The three main kinds are bronchiolitis - inflammation that involves the bronchioles (small airways); alveolitis - inflammation that involves the alveoli (air sacs); and vasculitis - inflammation that involves the small blood vessels (capillaries). More than 80 percent of interstitial lung diseases are diagnosed as pneumoconiosis, a drug-induced disease, or hypersensitivity pneumonitis. Some other types are idiopathic pulmonary fibrosis, bronchiolitis obliterans, histiocytosis X, chronic eosinophilic pneumonia, granulomatous vasculitis, Goodpasture's syndrome and pulmonary alveolar proteinosis. The cause of interstitial lung disease is not known, however, a major contributing factor is thought to be inhaling environmental pollutants. Other contributing factors include Sarcoidosis, certain drugs, radiation, connective tissue or collagen diseases and family history. Treatments may include corticosteroids, influenza or pneumococcal pneumonia vaccine but these are of limited effectiveness.

Many Occupational Lung Diseases are inflammatory in origin, arising from repeated and long-term exposure to certain irritants on the job. These include for example asbestosis, coal worker's pneumoconiosis (caused by inhaling coal dust), silicosis (caused by inhaling free crystalline silica), byssinosis (caused by dust from hemp, flax, and cotton processing, also known as brown lung disease), aluminosis,

anthracosis ("collier's lung", from the accumulation of carbon from inhaled smoke or coal dust in the lungs), asbestosis, chalicosis (stone-cutters' lung disease, due to inhaling stone dust), siderosis (occurring in iron workers, produced by the inhalation of particles of iron), tabacosis, hypersensitivity pneumonitis (caused by the inhalation of fungus spores from moldy hay, bird droppings, and other organic dusts and occupational asthma (caused by inhaling certain irritants in the workplace, such as dusts, gases, fumes, and vapors).

Pulmonary Sarcoidosis causes small lumps, or granulomas, which generally heal and disappear on their own. However, for those granulomas that do not heal, the tissue can remain inflamed and become scarred, or fibrotic. Pulmonary sarcoidosis can develop into pulmonary fibrosis. Bronchiectasis, a lung disease in which pockets form in the air tubes of the lung and become sites for infection, can also occur. Treatment may include the use of corticosteroids.

Stomatitis, inflammation of the mouth, and mucositis, inflammation of the mucosa can arise from sources as diverse as Candida albicans, dentures, chemotherapy and radiation therapy to the head, neck or mouth ("Radiation mucositis"). It may be secondary to infection, trauma, systemic diseases or autoimmune mechanisms. These come in many forms, such as aphthous ulcers, Acute Necrotizing Ulcerative Gingivitis i.e. "trench mouth", and Lichen Planus. Herpetiform ulcers treatment has ranged from antibiotics, immunosuppressants and yogurt, to Lactobacillus capsules, tetracycline and systemic steroids. Palliative measures include topical anesthetics, Vitamin E, analgesics, and coating agents. Antiviral agents may be used if viral origin is established.

Rhinitis is a reaction that occurs in the eyes, nose and throat when airborne irritants (allergens) trigger the release of histamine. Histamine causes inflammation and fluid production in the fragile linings of nasal passages, sinuses, and eyelids. The two categories of rhinitis are allergic rhinitis (seasonal and perennial) and nonallergic Rhinitis (including eosinophilic, rhinitis medicamentosa, vasomotor Rhinitis, neutrophilic rhinosinusitis, and others), which come from fumes, odors, temperature or atmospheric changes, smoke, etc. Treatments for nonallergic rhinitis include oral medications, inhaled medications, immunotherapy, and surgery for some conditions.

Wegener's Granulomatosis is a disease that usually begins as a localized granulomatous inflammation of upper or lower respiratory tract mucosa and may progress into generalized necrotizing granulomatous vasculitis and glomerulonephritis. The cause is unknown. Although the disease resembles an infectious process, no causative agent has been isolated. Treatment is with immunosuppressive cytotoxic drugs.

Pancreatitis is inflammation of the pancreas and can arise from abdominal trauma, or the formation of gallstones that obstruct the common bile duct. It can be associated with excessive ingestion of alcohol; with disorders such as cystic fibrosis or Reye's syndrome; or with scorpion stings. Infectious causes include mycoplasmas, Epstein-Barr viruses, Coxsackie viruses, leptospirosis, hepatitis viruses, mumps, congenital German measles, Ascaris worms, and syphilis. The inflammation per se is generally not treatable. Treatment is usually supportive and consists of the management of pain and intravenous feeding.

Neuroretinitis is inflammation of the retina and optic nerve of the eye ("optic neuritis"). It is often idiopathic. It frequently arises secondary to some kind of infection, such as Hepatitis B, HSV, EBV, influenza A, mumps, Coxsackie B, TB, salmonella, Lyme disease, syphilis, leptospirosis, Histoplasmosis, Toxoplasmosis, toxocara, Sarcoidosis and cat-scratch disease. Treatment is thus to the underlying cause. For example, Diffuse unilateral subacute neuroretinitis (DUSN) arises from nematodes deep in the retina or in the subretinal space. Anthelminthic treatment is then used. When the origin is Toxoplasmosis, then anti-Toxoplasma medications such as Pyrimethamine.

Other eye inflammations include scleritis and episcleritis, inflammation of tissues on the sclera; choroiditis, inflammation of the middle coat (choroid) of the eyeball, and uveitis, which is inflammation of the parts of the eyes that make up the iris.

Gastritis is inflammation to the stomach lining. Atrophic gastritis is characterized by the loss of the stomach cells that are responsible for manufacturing acid, pepsin, and intrinsic factor. This condition occurs in older people or those suffering from Helicobacter pylori. Erosive (hemorrhagic) gastritis occurs when shallow ulcers or sores develop on the upper layer of the stomach lining, usually because of the excessive ingestion of a stomach irritant such as aspirin or alcohol.

There can also be mentioned appendicitis, which can occur when a hard piece of stool blocks the opening of the appendix, causing swelling and inflammation.

The great majority of skin problems involve some type of inflammation, such as response to physical injury (e.g. sunburn, ticks, abrasion, or a bee string), acute allergic contact dermatitis (such as poison ivy), and infections (such as boils and cold sores). Ingrowing hairs, or pili incarnati, can cause acute pustular reactions. Cancerous lesions

of the skin frequently show some degree of inflammatory response. Acne's inflammation is caused by leakage of sebum and keratin debris outside the distended pilosebaceous duct. The bacillus Propionibacterium acnes, which populates the lesions, may also contribute indirectly to this inflammation by metabolizing the sebum to produce irritant fatty acids. Inflammation in skin problems is usually the result of the release of chemical mediators in the skin, notably histamine, peptides (kinins) and fatty acids (prostaglandins and leukotrienes), which are formed enzymatically in response to e.g. injury. Medications designed to counteract inflammation in the skin may or may not antagonize the effects of the particular type of mediator involved, if that is known. The inflammation can take many different forms, including redness, (from dilation of blood vessels); heat, (from increased blood flow); swelling (from leakage of fluid from the small blood vessels); whealing reactions (hives, nettle rash, urticaria) in which vascular changes predominate, and pain or itching. Blisters (from enzymes released from inflammatory cells, resident cells of the skin, or blood plasma components) can cause the breakdown of proteins responsible for the structural integrity of the skin, leading to serious inflammatory disorders such as pemphigus. In addition, the affected skin may feel indurated (hardened) because of the deposition of the coagulation protein fibrin and the infiltration by inflammatory blood cells (lymphocytes, histiocytes, and polymorphonuclear leukocytes).

Prostatitis, inflammation of the prostate, comes in several different forms, including those of bacterial origins, and those which are not, including chronic abacterial prostatitis and asymptomatic inflammatory prostatitis. Certain types of anti-

inflammatory agents, such as non-steroidal anti-inflammatory medications (Ibuprofen and naproxen) along with muscle relaxants can be used in the non-bacterial cases.

Cystic fibrosis (CF) is an inherited disease characterized by an abnormality in the glands that produce sweat and mucus. It is chronic, progressive, and is usually fatal. The basis for the problem with CF lies in an abnormal gene, which results in an atypical electrolyte transport system within the cells of the body. The abnormal transport system causes the cells in the respiratory system, especially the lungs, to absorb too much sodium and water. This causes the normal thin secretions in our lungs to become very thick and hard to remove. The high risk of infection in the respiratory system leads to damage in the lungs, lung that do not work properly, and eventually death of the cells in the lungs. The most common causes for infection in the lungs are Staphylococcus aureus, Haemophilus influenza and Pseudomonas aeruginosa (PA). The disorder itself is largely untreatable.

The above list is by no means complete, but demonstrates the extraordinary breadth of causes, mechanisms and treatment (or lack thereof) for inflammation.

Further, the prior art knows that there are many paradoxical features in the inflammation system. As an example, in lung inflammation, nitric oxide appears to be a pro-inflammatory mediator in acute situations e.g. ARDS but anti-inflammatory in more stable situations. As a second example, the cytokine TGF-beta-1 possesses both pro-inflammatory and anti-inflammatory activities. Virtually all cells have TGF-beta-1 receptors, and the cytokine has many other roles other than in inflammation. As a third example, CRF appears to have both pro-inflammatory and anti-inflammatory activities.

Applicants argue, "an inflammatory response is basically the same regardless of tissue." This is simply not true. If it were, treatments for inflammatory disorders would work regardless of the particular nature of the disease. Such is not the case, obviously, since many inflammatory disorders have no treatment. And it is not true as seen by the huge assortment of mediators.

In rebuttal, the examiner must also point out that these compounds are alleged, in both the remarks and the specification, to be inhibitors of IκB-α, although the data shows them to be somewhat weak in that regard (and non-existent for a few species tested). However, if true, that would indicate that these compounds would make inflammation worse, not better. In this regard, the Carlet, ADVANCES IN SEPSIS Vol 1 No 3 2001, page 93 reference is cited. Figure 1 shows that Corticosteroid anti-inflammatory treatment starts by activation of IκB-α, which then inhibits NF-κB. That is, IκB-α is an inhibitor of NF-κB; that inhibition causes decreased transcription for proinflammatory cytokines, COX-2, ICAM-1, VCAM-1 and increased transcription for IL-1ra. Thus, one wishes to activate IκB-α in order to get suppression of the proinflammatory cytokines, but these compounds are alleged to provide inhibition of IκB-α. Thus, any inflammatory disorder mediated by proinflammatory cytokines (which would include α-TNF, IL-1, IL-2, IL-4, IL-6, IL-8, IL-12, LT, IFN-α, INF-γ, and assorted chemokines), COX-2, ICAM-1, VCAM-1 would be made worse by this inhibition of IκB-α. This does not include all inflammatory disorders of course but does include many of them.

Claims 68-74 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one

skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The compounds are disclosed to be CDK2 inhibitors. There is no reason to think that one of ordinary skill in the art could, without undue experimentation, treat such difficult disorders with such compounds. Note the following:

I. References of record do not support such a notion. Glab(1994) does not mention therapeutic utility. Others present use only as a possibility to be achieved by developing much better compounds. For example, Vesely (1994) says, "It is possible that, through its specificity, olomoucine may lead to a compound which will preferentially inhibit the proliferation of certain tumor cells." Olomoucine is excluded by proviso from the claims. This shows that basic research is still required to obtain the necessary selectivity. Abraham (1995) says that "olomoucine may constitute a lead compound for the design of new anti-tumor agents." Similarly, Schultz-Gahmen (1995) referring to its results, says it "should prove useful in modifying and improving the lead compound." But, a lead compound is one which is not actually ready for use; it is by its nature something which needs to be modified by additional research. The traverse on this is not agreed with. Applicants cite what is "well known in the art". A reference will be needed to support this, showing that some particular CDK2 inhibitor has been established as effective for the scope or any or all of these rejected claims.

II. Although olomoucine itself is not potent enough to be effective, the testing presented in Table 7 established that many of these compounds are either less effective as CDK2 inhibitors than olomoucine, or are not effective to actually inhibit cell proliferation even in this crude test, or both. Indeed, a number of species displayed no measurable activity

in either test. Thus, in the first 7 on page 64, three of them have IC(50) values which are so high that they have no meaningful potency, and four had no demonstrated activity at all. The specification says that cell proliferation inhibition has an IC(50) of "preferably less than 0.5 μg/ml" which is a reasonable standard, but only 4 species met that standard; the other 20 species tested did not. Even on this very simple *in vitro* test, the results show that most compounds are ineffective. Applicants argue that the examiner has not supported his doubts, but those are the very facts which justify the doubts. Applicants are claiming vastly more than has ever been made to work for olomoucine, using compounds which are for the most part weaker than olomoucine.

III. The inclusion of gout in claim 83 makes no sense at all. Patients with gout are normally told to avoid high purine foods, in order to reduce uric acid secretion. The traverse is unpersuasive, and does not deal with the issue raised. Instead, the argument appears to be that these compounds will "reduce the number of proliferating clones of immunocytes", but there is no evidence whatsoever that this is true.

IV. Systemic lupus erythematosus (SLE) is a complex disorder, an autoimmune disease characterized by immune dysregulation resulting in the production of antinuclear antibodies (ANA), generation of circulating immune complexes, and activation of the complement system. It is a difficult disorder which can be fatal. Applicants point out that treatments include anti-neoplastic agents. This is true, methotrexate is used. But so far as the examiner is aware, methotrexate is not a CDK-2 inhibitor. It is true that cell growth is involved in Lupus. However, cell growth is involved in the vast majority of diseases, so by this reasoning, applicants compounds would be effective for most diseases, period. Applicants have presented no nexus between SLE and CDK-2

inhibition. The same is true for MS. Multiple Sclerosis (MS) is a chronic disease of the central nervous system. Viral and autoimmune etiologies have been postulated. While genetic and environmental factors are known to contribute to MS, the skill level in this art is so low that a specific cause for this disease has not been not identified. Corticosteroids, Interferonß-1B (Betaseron) as well as Interferonß-1a have been used with some limited success. However, so far as the examiner is aware, a) CDK-2 inhibitors have not been successfully employed against MS and b) immunosuppressive agents have not been convincingly established as effective against MS. A great deal of research has gone into the use of immunosuppressive agents for MS, but their use remains very controversial. However, applicants have not established that their compounds actually are immunosuppressive agents.

V. As set forth in the rejection of claim 68 above above, the claim 68 (and 70) language is extremely broad. No pharmaceutical could possibly have such a range.

VI. It is noted that this case discloses an additional property (not present in original parent 08/692012) which "some of the compounds of this invention" (page 3, line 8) have, viz, inhibition of IκB-α kinase. However, it is noted that a) it is unclear which compounds actually have this property, aside from the ones tested on page 56 b) it is not asserted that any of the utilities in these rejected claims are connected to this property. Note in this regard the discussion of the Carlet reference above.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-2, 8, 10, 14-16, 18, 20, 44-48 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 5866702. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims here are just broader versions of those of the grandparent case.

Specification

The parentage is still not correct. It says "... which is a section 371 application of ..." but in fact, it is a CIP of the PCT application.

This case lacks a proper abstract; the one provided is too brief as to structure of the compounds. Some definitions are needed for variables.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 703-308-4718. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached on 308-4716. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 708-308-1235.

Mark L. Berch
Primary Examiner
Art Unit 1624

September 6, 2002